Selective Estrogen Receptor Modulators and Prevention of Invasive Breast Cancer

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THIS YEAR, MORE THAN 200 000 WOMEN IN THE UNITED States will be diagnosed as having invasive breast cancer.[1] The past 20 years of research translating an understanding of basic biology into therapeutics has led to major improvements in the survival and quality of life of patients who carry a diagnosis of breast cancer. Parallel strategies to prevent breast cancer have also been studied. These include lifestyle modification (eg, diet, alcohol intake, optimizing weight, exposure to exogenous estrogens), ablative surgery (prophylactic mastectomy, oophorectomy, or both), and more recently, chemoprevention with selective estrogen receptor modulators (SERMs) such as tamoxifen.

More than 30 years ago, tamoxifen entered clinical trials and demonstrated significant antitumor activity in patients with advanced breast cancer. Understanding of what characterized the type of patient and the types of tumors that would benefit from tamoxifen was refined with an understanding of estrogen receptor biology and an ability to measure estrogen receptor status. Animal experiments with tamoxifen forecasted improved outcomes in patients with operable, early stage breast cancer and reduced probability of developing a second breast cancer.

Although there was compelling evidence that tamoxifen could reduce the risk of recurrence and improve survival in patients with early stage breast cancer, particularly with longer duration of therapy, serious concerns were raised regarding the toxicity of long-term therapy. These concerns focused on the development of liver tumors in rats and an increased incidence of endometrial cancer in women receiving tamoxifen.[2] After prolonged deliberation regarding subjecting healthy women to such risks and after scrutiny of all available data, the first prevention trials with tamoxifen were launched in the United States and Europe about 15 years ago.

One of these trials, conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), found that compared with placebo, tamoxifen reduced the relative risk of invasive and noninvasive breast cancer by about 50%.[3] The beneficial effect of tamoxifen was most striking in reducing the relative risk of estrogen receptor–positive breast cancer (69%), as well as the relative risk of invasive breast cancer among women with a history of atypical hyperplasia (86%) and lobular carcinoma in situ (56%). Competing with the apparent benefits of tamoxifen in this population of otherwise healthy women was an increased relative risk (RR) of endometrial cancer (RR, 2.53), thromboembolic disease (RR, 3.01), deep vein thrombosis (RR, 1.60), and stroke (RR, 1.59).[3-6] The major toxicities were considered potentially to offset the prevention benefit of tamoxifen, particularly in older patients. Despite differences in trial size, methods, and eligibility of participants in other tamoxifen prevention studies, a meta-analysis of these trials demonstrated that tamoxifen reduced the relative risk of breast cancer incidence by approximately 40%.[7]

Yet, despite a clear indication and US Food and Drug Administration approval for use of tamoxifen to prevent breast cancer, relatively few eligible women receive tamoxifen as a preventive strategy today.[5] Reasons for this are multifactorial but include the view of some physicians regarding competing risks and benefits, potential tamoxifen recipients not understanding the data from tamoxifen prevention trials, underestimation of the risk of developing breast cancer, and overestimation of the risks associated with tamoxifen. Patients' underestimation of the personal risk for disease and overestimation of the prospects for good health are common in other conditions.[8,9] Media attention to breast cancer may make it a special exception, but the breast cancer exception may apply selectively to younger women, who tend to exaggerate their risk of getting breast cancer. Older women are far more likely than their younger counterparts to be candidates for SERM chemoprevention but may not view their personal risk of breast cancer with sufficient worry to justify a commitment to long-term daily medicine that carries its own competing risks and adverse effects. The latter concern is amplified because the physicians in a position to prescribe tamoxifen for prevention purposes are frequently nononcologists with little familiarity with the drug.

See also pp 2727 and 2742.

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Clearly tamoxifen as a prevention agent was a significant step, but only the first.

In this issue of *JAMA*, Vogel and colleagues[10] report the first efficacy and safety results from the NSABP's second breast cancer prevention trial. In a companion article, Land and colleagues[11] report the findings from a thorough patient-reported outcomes study conducted in a subgroup of participants in this same trial. The trial, known familiarly as STAR (Study of Tamoxifen and Raloxifene), compared tamoxifen, 20 mg/d, vs raloxifene, 60 mg/d, over 5 years. Although tamoxifen has long been appreciated as a chemoprevention agent, raloxifene was only recently reported to be superior to placebo in preventing breast cancer (but not in reducing coronary risk), as announced by the RUTH (Raloxifene Use for The Heart) trial investigators.[12]

Considerable speculation and preclinical and observational evidence surrounded the hope that raloxifene, a second-generation SERM known and used fairly widely to prevent osteoporosis and fractures, would be associated with less uterine hyperplasia and cancer than tamoxifen. This might help raloxifene emerge as a clear choice for breast cancer prevention based on safety, even if efficacy were equal. Perhaps primary care physicians and gynecologists would be more comfortable prescribing long-term raloxifene to healthy women who wish to decrease their probability of getting breast cancer. Indeed, the not-outrageous hope for multibenefit SERM therapy after menopause, reducing the burdens of osteoporosis, cancer, and even heart disease with one daily pill, led some to suggest that prevention of breast cancer should perhaps not be the primary target of large-scale SERM therapy. Instead, there may be hope for a family of benefits, thanks to the "s" (ie, "selective") in SERM.

The STAR trial focused on breast cancer as the primary end point, and the 2 agents showed no statistically significant difference in its prevention. These treatments were not associated with differences in death from any cause, other invasive cancers, ischemic heart disease, or osteoporotic fractures. Raloxifene was associated with slightly fewer thromboembolic events and fewer hysterectomies, cataracts, and cataract surgeries, whereas tamoxifen was associated with a trend toward fewer cases of noninvasive breast cancer. This last observation is not easily reconciled, nor are the downstream clinical consequences of this differential effect known. Specifically, it is not yet known whether the greater number of noninvasive cancers in women receiving raloxifene translates into the need for more surgery, follow-up biopsies, radiation therapy, and ultimately more invasive breast cancers.

The STAR symptom and quality-of-life data revealed a striking similarity between treatments in physical and mental health, including depression.[11] There were some small differences between treatments in some of the reported adverse effects, but these differences rarely if ever exceeded a range usually considered clinically significant. The authors suggest that group differences with effect sizes in the range of 0.2 to 0.4 may be clinically significant. While this may be true, it is impossible to know without corroborating clinical evidence (ie, anchors against which to calibrate the difference). Without such anchors, a more reasonable and commonly shared minimum effect size for clinical significance is 0.5,[13] a magnitude never reached across multiple comparisons in this study. In short, the most defensible conclusion is that the quality of life and the adverse-effect burden of raloxifene and tamoxifen are comparable.

Although the authors suggest that "these results can be widely used as tools in decision making or in helping a patient anticipate and cope with the sequelae of her chosen agent,"[11] an unresolved issue is how clinicians can do that. From the perspective of the quality-of-life data, the first step would be to emphasize that, regardless of SERM choice for prevention, overall physical and mental health might worsen modestly in the beginning of therapy, but the risk of this is slight and no different between choices. Sexually active women who value this aspect of their lives may prefer tamoxifen over raloxifene, and women who wish to avoid leg cramps or vaginal bleeding/discharge might prefer raloxifene. Patient interest in discussing symptoms related to weight gain, bladder control, or vasomotor symptoms might generate further discussion, but in all cases the proportion of women who reported symptom severity "quite a bit" or "very much" was universally low and differences between groups were small.

Perhaps a better understanding of barriers to chemoprevention is needed. As Land et al[11] report, patient-reported outcomes are important in the chemoprevention setting because women must choose between taking an agent with certain cost and possible adverse effects vs living in a healthy, medicine-free state with an increased risk of cancer. Even with the choice to accept therapy, the probability that breast cancer treatment will benefit any given individual is very low. Could this be why 4 of 5 women who screened eligible (almost 80 000 of them) chose not to participate? Another issue is why most women who started treatment stopped it in just over 3 years. A good number of these women stopped taking their study drug because of adverse effects. Knowing which women will do so will help design a more "tolerable" prevention strategy by better anticipating and treating patient-reported adverse events. The wealth of data available from this trial can shed light on some important barriers to initiating and sustaining a course of chemoprevention.

Other issues remain in the conduct of large-scale prevention trials, including the prospect of identifying a target population of women at higher risk. Only 331 breast cancers occurred among the 19 747 women participating in the STAR trial.[10] Applying the results of prevention trials to an individual using the Gail model, as opposed to a large population, may not be a particularly good discriminator. Preventive agents for widespread use in an otherwise healthy population need to be virtually devoid of significant ad-

verse effects. Decision making for an individual patient who is considering a preventive agent to reduce the risk of breast cancer must also take into account other health issues that may very well outweigh the risk of developing breast cancer. The NSABP P-1 and P-2 prevention trials were largely comprised of white women with relatively little representation from minority populations. Therefore, it is not known whether SERMs act differently across diverse ethnic subpopulations. The NSABP has outlined an ambitious strategy to increase underrepresented populations in future prevention trials. Further data are needed as to whether there is a differential effect on breast cancer incidence between tamoxifen and raloxifene in women who are *BRCA1*/*BRCA2* mutation carriers.[14] The large-scale prevention strategies conducted to date have focused on postmenopausal women. Strategies need to be developed for at-risk premenopausal women. For now, the NSABP has proposed to follow the STAR trial with a comparison of raloxifene with an aromatase inhibitor.[2] In Europe, an aromatase inhibitor is being compared with placebo in women at increased risk of developing breast cancer.[2]

The results of the STAR trial offer a pragmatic stepping stone to the next prevention trial in breast cancer. Raloxifene, if not superior to tamoxifen, may be more acceptable to clinicians presenting the option of a preventive drug. Although media coverage of the early release of data from the STAR trial suggest a clear "winner" in raloxifene, the data from clinical end points and patient-reported symptoms suggest a less clear conclusion. Assuming US regulatory approval of raloxifene to prevent breast cancer, physicians should discuss these 2 similar options carefully with their eligible and interested patients. Although women receiving raloxifene had significantly less uterine hyperplasia, there was not a statistically significant difference between groups in the incidence of endometrial cancer. The incidence of other malignancies, ischemic cardiac events, strokes, and fractures was not statistically different between the groups.

The breast cancer chemoprevention sky now includes 2 shining STARs—tamoxifen and raloxifene. Although neither is a supernova, their benefits include prevention of breast cancer in postmenopausal women at increased risk and, in the case of raloxifene, reduction of fractures related to osteoporosis. Perhaps because the clear benefits are limited to these end points, the relatively modest adverse event profiles and minimally impaired quality of life experienced by these women still may not be enough to convince primary care physicians to be more aggressive than they have been to date in breast cancer chemoprevention. Time will tell.

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